REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of the Claims

Claims 4 and 42 were previously cancelled. Claim 13 has been amended to clarify that the surface stabilizers are nonionic, anionic, cationic, and zwitterionic. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-3, 5-41 and 43-108 are pending, with claims 8, 15-16, 23-27 and 48-108 withdrawn from examination.

II. Provisional Double Patenting Rejections

The Examiner sets forth extensive provisional nonstatutory obviousness-type double patenting rejections, which are enumerated below for easy reference. Applicants respectfully traverse each ground of the rejection.

Rejection 1: Claims 1-3, 5-6 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 51, 60-61 and 64 of copending Application No. 12/320,431.

Rejection 2: Claims 1-3, 5, 11-12 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-5, 8-10, 15 and 17 of copending Application No. 12/292,092.

Rejection 3: Claims 1, 5-7, 10-14, 33-36 and 39-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 51, 60-61 and 64 of copending Application No. 12/117,982.

Rejection 4: Claims 1-3, 5-7, 9, 13-14 and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-17 of copending Application No. 12/052,436.

Rejection 5: Claims 1, 5 and 12-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 10-12 and 19 of copending Application No. 12/051,448.

Rejection 6: Claims 1, 5-7, 9-11, 13-14, 21-22, 28-41 and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-23 of copending Application No. 11/980,719.

Rejection 7: Claims 1, 5-6, 9, 11-14 and 44-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-4, 6, 8, 13-14 and 16-20 of copending Application No. 11/979,253.

Rejection 8: Claims 1, 5-7, 9, 11-14, 20, 28-31, 33-41 and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-3 and 5-19 of copending Application No. 11/761,900.

Rejection 9: Claims 1, 5-7, 9-11, 13-14, 20-22, 28-32, 33-40 and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-14, 17-19 and 21-23 of copending Application No. 11/436,887.

Rejection 10: Claims 1-2, 5-7, 9-10 and 13-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 3-5, 9 and 18-21 of copending Application No. 11/376,553.

Rejection 11: Claims 1, 5-7, 9-14, 18-21, 28-29 and 39-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-6, 8-9, 11-13, 15-16, 18-20, 24 and 27 of copending Application No. 11/275,069.

Rejection 12: Claims 1, 5-7, 9-12, 14, 18-22, 28-29, 31, 33-41 and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 9-12, 15-17 and 20-31 of copending Application No. 10/912,552.

Rejection 13: Claims 1, 5-7, 9-14, 18-22, 28-29 and 33-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-10, 12-24, 30, 34-35 and 38-39 of copending Application No. 10/895,405.

Rejection 14: Claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-38 of copending Application No. 10/768,194.

Rejection 15: Claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-25 and 36-39 of copending Application No. 10/701,064.

Rejection 16: Claims 1, 5-7, 9-14, 17-22, 28-41 and 43-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-31, 36-38 and 40 of copending Application No. 10/697,703.

Rejection 17: Claims 1, 5, 9 and 13-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of copending Application No. 10/317,948.

Rejection 18: Claims 1, 5-7, 9-14, 18-22, 28-29 and 33-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-32 of copending Application No. 11/928, 250.

Rejection 19: Claims 1, 5-7, 9-14, 28-29, 33-41 and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 4-19 and 21-32 of copending Application No. 11/367,716.

Rejection 20: Claims 1, 5-7, 9-14, 17-22 and 33-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of copending Application No. 10/784,900.

The guidelines concerning nonstatutory obviousness-type double patenting rejection as set forth in MPEP 804 II B 1 are excerpted below:

> *...[T]he analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. §103(a) obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).*
>
> *Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. §103(a) rejection, the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. §103(a) are employed when making an obvious-type double patenting analysis. These factual inquiries are summarized as follows:*
>
> *(A) Determine the scope and content of a patent claim relative to a claim in the application at issue;*
>
> *(B) Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;*
>
> *(C) Determine the level of ordinary skill in the pertinent art; and*

(D) Evaluate any objective indicia of nonobviousness.

The conclusion of obviousness-type double patenting is made in light of these factual determinations.

Any obviousness-type double patenting rejection should make clear:

(A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of the invention defined in a claim in the patent.

The rejection falls short of establishing the initial burden of a *prima facie* case of obviousness because the double patenting rejections fail to set forth a clear articulation of an analysis in support of each of the twenty obviousness-type double patenting rejections. Specifically, the Examiner fails to set forth the Graham inquiries or the additional considerations mandated by the MPEP. For example, none of the rejections explain the difference between the pending claims and the alleged conflicting claims. Conclusory statements cannot replace factual analysis in support of a *prima facie* case of obviousness. For this reason alone, withdrawal of the rejections is requested.

Applicants further request withdrawal of the rejections in view of the reasons below. For ease of discussion, the twenty rejections are grouped into three groups based on the rejection rationales: (A) claimed species/subgenus allegedly being obvious over disclosed genus, as in Rejections 1 and 4; (B) claimed invention allegedly being obvious by simple substitution of an element of the prior art, as in Rejections 2-3, 5-6, 8-9 and 11-20; and (C) others, as in Rejections 7 and 10.

A. Species *vs.* Genus

In Rejections 1 and 4, the Examiner contends that the compositions comprising a genus of the active agent render the claimed compositions comprising the species/subgenus of triamcinolone drug particles obvious.

MPEP 2144.08 sets forth the guidelines for the Examiner to determine whether one of ordinary skill in the art would have any reason to select the claimed species/subgenus in view of the broader, general teaching of a genus. Specifically, the MPEP requires the Examiner to consider the following aspects, where applicable:

(a) consider the size of the genus;

(b) consider the express teachings:

(c) consider the teachings of structural similarity;

(d) consider the teachings of similar properties or uses;

(e) consider the predictability of the technology; and

(f) consider any other teaching to support the selection of the species or subgenus.

The Examiner fails to provide an analysis concerning each of the points above to support the notion that the subgenus of triamcinolone drug particles in the claimed invention would have been obvious in view of the genus of drug particles of the alleged conflicting claims.

The MPEP 2144.08 further requires that "[w]hen a single prior art reference which discloses a genus encompassing the claimed species or subgenus but ***does not expressly disclose the particular claimed species or subgenus***, Office personnel should attempt to find ***additional prior art*** to show that the differences between the prior art primary reference and the claimed invention as a whole would have been obvious" (emphasis added).

In the present case, the Examiner fails to bridge the gap between a broad genus of drug particles and the subgenus of triamcinolone drug particles in the absence of any secondary

reference, let alone to articulate a reason to select the claimed species from the teaching of the secondary reference.

In view of the foregoing, Rejections 1 and 4 lack any valid basis and should be withdrawn.

B. "Simple Substitution"

In Rejections 2-3, 5-6, 8-9 and 11-20, the Examiner asserts that one of ordinary skill in the art would have substituted the active agent of the alleged conflicting claims for triamcinolone of the claimed invention. The reason provided by the Examiner is that either the active agent belongs to the same drug category or the substitution can be made in view of the teaching of U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge").

The U.S. Supreme Court's decision, *KSR International Co. v. Teleflex Inc.*, prompted a reconsideration of the simple substitution rationale, *i.e.*, positing the obviousness by simple substitution of one known element for another to obtain predictable results. *See* the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Register*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines." Pursuant to the Guidelines, an examiner seeking to advance a simple substitution rationale is obliged to articulate:

(1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;
(2) a finding that the substituted components and their functions were known in the art;
(3) a finding that one of ordinary skill in the art could substituted one known element for another, and the results of the substitution would have been predictable; and
(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the faets of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness for the lack of an analysis of any of the above aspects. In particular, the Examiner has not established any predictability, i.e., at the time of filing, how one skilled in the art could predict that a stable nanoparticulate triamcinolone composition can be made in view of the absence of any structural similarity between triamcinolone and the active agent of the alleged conflicting claims. Moreover, the Examiner's assertion of simple substitution directly contravenes the explicit teaching of the present application that "not every combination of surface stabilizer and active agent will result in a stable nanoparticulate active agent composition" (page 16, paragraph [0049]). This unpredictability is also supported by the teaching of Liversidge. See, for example, column 7, lines 21-23 and columns 14-15, Comparative Examples A-F.

In view of the foregoing, withdrawal of Rejections 2-3, 5-6, 8-9 and 11-20 is warranted.

C. Other Rejections

Rejection 7 is based on the ground that "the claimed invention teaches a broad genus of a composition containing a subgenus of triamcinolone drug particles whereas Ryde '253 teaches a subgenus of a low viscosity liquid dosage containing a broad genus of active agent particles" (Office Action, page 10, lines 9-11).

This ground of rejection is unclear because the Examiner fails to lay out any analysis in support of the conclusion. If the Examiner attempts to reject the claims on the ground of "genus *vs.* species," the rejection should be withdrawn in view of the discussion under Section A.

Otherwise, Applicants respectfully request the Examiner to substantiate the rejection by a detailed analysis as required by the MPEP.

Rejection 10 is based on the ground that "it would have been well within the purview of the skilled artisan to add a leukotriene receptor antagonist to the instant composition depending on the targeted or desired treatment" (Office Action, page 13, lines 10-12).

Again, without any rationale to support the rejection, Applicants fail to appreciate: (i) why one skilled in the art would have been motivated to add a leukotriene receptor antagonist; and (ii) how one skilled in the art would have obtained the composition as prescribed in claim 1 by adding a leukotriene receptor antagonist. Therefore, withdrawal of the rejection or further clarification is respectfully requested.

III. Rejection of Claims under 35 U.S.C. §103(a)

Claims 1-3, 5-7, 9-14, 17-22, 28-41 and 43-47 are rejected under 35 U.S.C. §103(a) for alleged obviousness over U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge") in view of U.S. Patent No. 5,916,596 to Desai et al. ("Desai"). Applicants respectfully traverse the rejection.

A. Prior-art disclosure of a genus does not render the claimed species obvious.

Liversidge describes particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface of the drug particles to maintain an effective average drug particle size of less than 400 nm. *See* abstract. Liversidge further discloses over 40 categories of drugs, but does not explicitly mention triamcinolone, which is required by the claimed invention. *See* Liversidge, column 3, line 53, through column 4, line 14.

In an attempt to remedy the deficiency of the primary reference, the Examiner cites Desai for the alleged teaching of triamcinolone as an active agent because "Desai et al. was provided to

demonstrate that triamcinolone acetonide is a poor[ly] soluble drug" (Office Action, page 27, lines 13-14).

As discussed *supra*, MPEP 2144.08 requires the Examiner to consider the following aspects, where applicable:

(a) consider the size of the genus;
(b) consider the express teachings:
(c) consider the teachings of structural similarity;
(d) consider the teachings of similar properties or uses;
(e) consider the predictability of the technology; and
(f) consider any other teaching to support the selection of the species or subgenus.

Concerning point (a), in addition to Liversidge's disclosure of over 40 categories of drugs without explicit disclosure of triamcinolone, Desai describes an enormous number of water insoluble pharmacologically active agents, spanning columns 11-14. Neither reference has any suggestion to preferentially select triamcinolone or the drug category that it belongs to.

In relation to point (b), Liversidge does not disclose triamcinolone, let alone any express teaching of selecting triamcinolone as the active agent. Desai lacks any express teaching of selecting triamcinolone as triamcinolone is buried in a 2-page long compound list. Therefore, one skilled in the art would not have had any reason to select triamcinolone as the active agent to obtain the claimed composition in view of the cited references.

Turning to points (c) and (d), the over 40 categories of drugs described by Liversidge and the numerous compounds disclosed by Desai do not necessarily share any structural similarity or have similar properties or uses.

In the absence of any guidance from the cited art to select the particular active agent of the claimed composition, the Examiner has fallen into the trap of hindsight distortion, *i.e.*,

breaking the claims down to their component elements, searching for each element in the prior art, and then putting the elements back together using Applicants' claims as a road map. As such, it is only by the improper reliance on this impermissible hindsight that the Examiner identified the specific elements in the references and formulated the combination of the elements necessary to obtain the claimed composition. *See Ortho-McNeil Pharmaceutical Inc., v. Mylan* (Fed. Cir. 2008) at 10 ("[i]n other words, Mylan's expert, Dr. Anderson, simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious. Of course this reasoning is always inappropriate for an obviousness test based on the language of Title 35…").

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness because the articulated rejection lacks valid support in the cited art.

B. A reasonable expectation of success is lacking.

The claimed invention relates to a nanoparticulate triamcinolone composition comprising, *inter alia*, particles of triamcinolone or a salt thereof. As acknowledged by the Examiner, Liversidge does not disclose triamcinolone. *See* Office Action, page 27, lines 4-5.

To bridge the gap between the claimed invention and the teaching of the primary reference, the Examiner relies on the secondary reference, Desai, for the alleged teaching of triamcinolone. At most, the Examiner attempts to apply an "obvious-to-try" rationale that is improper under the statute and governing case law.

Pursuant to the Court's ruling in *KSR*, to reject claims based on an obvious-to-try rationale must articulate all of the following:

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

In the present instance, at the time of filing, there was no reasonable expectation of successfully obtaining a stable nanoparticulate triamcinolone composition.

Both Liversidge and the present application point to the fact that "not every combination of surface stabilizer and active agent will result in a stable nanoparticulate active agent composition." *See* Liversidge, column 7, lines 21-23 and comparative Examples A-F, columns 14-15; and specification, page 16, paragraph [0049].

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

IV. Rejection of Claims under 35 U.S.C. §112, second paragraph

Claim 14 is rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse the rejection.

Claim 13 has been amended to include nonionic surface stabilizers of which the recitation of poloxamers and decanoyl-N-methylglucamide surfactants of claim 14 fall within. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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